CHAPTER 2

DEVELOPMENT OF CLINICAL PRACTICE GUIDELINES FOR SUPPORTIVE CARE IN CHILDHOOD CANCER – PRIORITIZATION OF TOPICS USING A DELPHI APPROACH

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2.1 ABSTRACT

INTRODUCTION

Currently, very few guidelines for supportive care for children with cancer exist. In the Netherlands, nationwide guidelines are over 10 years old and mostly based on expert opinion. Consequently, there is growing support and need for clinical practice guidelines (CPGs), which ought to be developed with a well-defined methodology and include a systematic search of literature, evidence summaries and a transparent description of the decision process for the final recommendations. Development of CPGs is time consuming, therefore it is important to prioritize topics for which there is the greatest clinical demand.

OBJECTIVES

To prioritize childhood cancer supportive care topics for development of CPGs.

METHODS

A Delphi survey consisting of two rounds was conducted to prioritize relevant childhood cancer supportive care topics for the development of CPGs. A group of experts comprising 15 pediatric oncologists, 15 pediatric oncology nurses and 15 general pediatricians involved in care for childhood cancer patients were invited to participate. All relevant supportive care topics in childhood cancer were rated.

RESULTS

In both rounds, 36 panelists (82%) responded. Agreement between panelists was very good, with an intraclass correlation coefficient of 0.918 (95% CI = 0.849-0.966, $p<0.001$) in round 2. The 10 topics with the highest score in the final round were infection, sepsis, febrile neutropenia, pain, nausea/vomiting, restrictions in daily life and activities, palliative care, procedural sedation, terminal care and oral mucositis.

CONCLUSION

We successfully used a Delphi survey to prioritize childhood cancer supportive care topics for the development of CPGs. This is a first step towards uniform and evidence-based Dutch guidelines in supportive care in childhood cancer. Even though performed nationally, we believe that this study can also be regarded as an example starting point for international development of CPGs in the field of supportive care in cancer, or any other field for that matter.

2.2 INTRODUCTION

The current high survival rates for children with cancer of 75%-80% are the results of the introduction of intensive treatment protocols consisting of surgery, radiotherapy and chemotherapy.[1] However, some of these treatment strategies cause severe adverse effects that can lead to treatment-related death. A study among children with acute lymphoblastic leukemia found treatment-related death to be ranked as the second leading cause of death, after cancer itself.[2] In addition, adverse effects might lead to delay of treatment or dose reduction of chemotherapy, which causes suboptimal treatment and might thus also lower survival chances. Moreover, as shown in children with acute myeloblastic leukemia, these adverse effects might lead to vast morbidity and a decreased quality of life.[3] Supportive care focuses on the prevention and management of these adverse effects of cancer and its treatment. Thus, optimal supportive care is needed to reduce and/or prevent morbidity and mortality and to improve quality of life for children with cancer and their families.[4,5]

To ensure that childhood cancer patients receive optimal care, CPGs are essential.[6,7] CPGs are defined as *"statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."*.[8] CPGs aim to bridge the gap between research and clinical practice and are regarded as powerful tools to improve the quality of care.[9-11] In addition, CPGs can contribute to a reduced variability in daily practice and costs.[6,7,12]

In the Netherlands national guidelines for supportive care are over 10 years old and are mostly based on expert opinion.[13] Every clinic and sometimes even every individual care provider can make their own choices regarding optimal supportive care interventions. This can result in conflicting recommendations for healthcare providers, children with cancer and their parents and thus in suboptimal care. In addition, clinical practice variation is associated with increased health care costs.[14]

Internationally, evidence based guidelines regarding supportive care in childhood cancer are sparse as well. The few that exist are aimed at specific areas of the major supportive care topics, e.g. nausea and vomiting, and febrile neutropenia.[15-18] However, from personal experience and contacts with colleagues abroad we know that the will to develop CPGs regarding supportive care in childhood cancer not merely exists in the Dutch Childhood Oncology Group (NL), but also in multiple international guideline groups, among others the Children's Oncology Group (US), the C^{17} Council (CA), the

Pediatric Oncology Group of Ontario (CA), the Children's Cancer and Leukaemia Group (GB) and the Swiss Paediatric Oncology Group (CH).

For guidelines to be of optimal use, it is of utmost importance to develop them via a vast methodology, base them on summaries of the best available evidence, clearly distinct between weak and strong recommendations and include appropriate recognition for shared decision making, i.e. acknowledge patient values and preferences.[19]

Therefore, we have initiated a project for the development of CPGs for supportive care in childhood cancer. As the development of CPGs is time consuming and supportive care is a very extensive field, a first step was to identify and prioritize supportive care topics for which there is the greatest clinical demand. To achieve this, we conducted a Delphi survey among professionals in the field of childhood cancer.

2.3 METHODS

DELPHI APPROACH

The Delphi approach is a well-known method for reaching consensus in a group and relies on anonymity, iteration, controlled feedback and statistical group response.[14] In multiple rounds incorporating feedback of the groups' response, participants compile a consensus list.

SELECTION OF CORE RESEARCH TEAM

Before commencing this study, a core research group was formed to guide the process of the Delphi survey. This group comprised seven members: two pediatric oncologists, one pediatrician trained in epidemiology, one pediatrician involved in care for childhood cancer patients in a shared care center, one pediatric oncology nurse, one postdoctoral scholar and one PhD student (MD). The core research group formed the initial list of relevant topics; each member was asked to individually form a list of all supportive care topics he or she could think of, subsequently these were all incorporated into the final list. Also, the core research group decided on the number of rounds of the survey and discussed the outcome of each round.

SELECTION OF PANELISTS

For this Delphi survey, we invited various professionals from all over The Netherlands; 15 pediatric oncologists and 15 pediatric oncology nurses from all seven Dutch childhood oncology centers. Furthermore, 15 general pediatricians involved in care for childhood cancer patients from various Dutch shared care centers were invited.

DELPHI SURVEY

The list of relevant topics, as formed by the core research team, was incorporated in a Delphi survey to determine the order of development of CPGs for all topics in supportive care in childhood cancer. This survey was sent to all panelists by e-mail, with the option to send it back digitally or per mail. In both rounds, two weeks after the initial distribution e-mail reminders were sent to all non-responders, two weeks later we attempted to contact all non-responders personally, by phone or by e-mail.

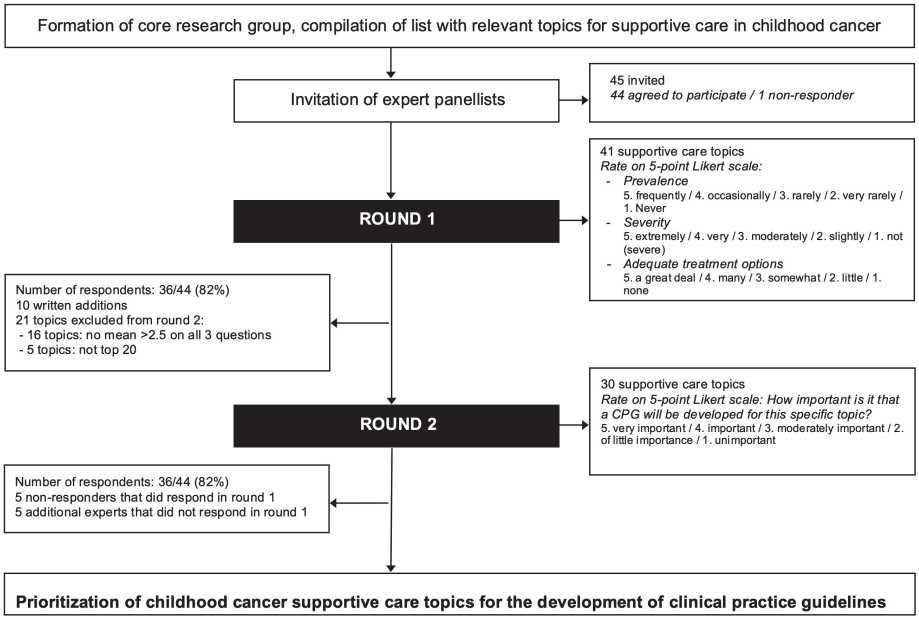

Figure 2.1. Outline of the Delphi approach.

In Figure 2.1 the Delphi approach is shown. In the first Delphi round, panelists were asked to rate prevalence, severity and adequate treatment options for each supportive care topic on a 5-point Likert scale ranging from one (low ranking) to five (high ranking). The panelists also had the option to provide written comments and to suggest missing topics (see Supplemental material 2/S1). For the second Delphi round, only topics were selected that had mean scores of >2.5 on all three questions in round one. This was chosen because we wanted to start supportive care guideline development with topics that are clinically most relevant, which we regarded as occurring often, being relatively severe and having adequate treatment options. Of these, the 20 highest scoring topics were selected and presented in descending order in the second Delphi round (see

Supplemental material 2/S1). This was limited to the 20 highest scoring items as we wanted our questionnaires to be focused on the most important topics to start CPG development with, and minimize the risk of causing fatigue (and thus perhaps non-response) in our panelists. Also, all written additions were included. In this second round the panelists were asked to rate how important it is that a CPG will be developed for the specific topic, on a 5-point Likert scale ranging from one (unimportant) to five (very important). Before commencing our survey, the core research group decided to initially limit the number of rounds to two, as this Delphi survey had a prioritizing rather than a selective character. We decided to consider more rounds when there was no agreement between panellists. Each questionnaire took less than 15 minutes to complete.

ANALYSIS

We explored agreement between panelists. We determined there was agreement when more than 66% of all panelists rated a four or five on the 5-point Likert of a specific topic. In addition, the level of agreement between panelists was estimated with the intraclass correlation coefficient (ICC), set to a two-way mixed model with absolute agreement. [20] As our study involved several panelists, we present the average measure ICC, with 95% confidence interval (CI) and p-value. Cut-off values for ICC are arbitrary, but similar to kappa statistics agreement was categorized as poor (ICC <0.2), fair (ICC 0.3-0.4), moderate (ICC 0.5-0.6), good (ICC 0.7-0.8) or very good (ICC >0.8).[21]

Statistical analyses were performed using IBM SPSS Statistics version 22.0 (International Business Machines Corporation, NY, USA).

2.4 RESULTS

Between July 2013 and December 2013, panelists completed a series of two questionnaires. A total of 45 experts were invited to participate of whom 44 responded and were willing to do so. Round one of the Delphi survey consisted of 41 topics and comprised the full initial list of supportive care topics, as formed by the core research group (Table 2.1). The response rate in round one was 82% (36/44 experts). Five experts passively dropped out of the panel after round one, i.e. did not respond to several reminders for round two. In the second round, five experts that did not return round one did participate in this round. Thus, the response rate in round two was also 82% (36/44 experts). In all, the panel returning round two consisted of 14 pediatric oncologists, 11

pediatric oncology nurses and 11 general pediatricians involved in care for childhood cancer patients.

Table 2.1. Results of the Delphi survey round one, sorted by descending overall mean score on all three items.

	Mean score†			
Supportive care topic	Prevalence	Severity	Adequate treatment options	Overall mean score
Anemia‡	4.50	2.89	4.72	4.04
Infection‡	4.28	3.78	4.02	4.03
Nausea / vomiting‡	4.69	3.25	4.02	3.99
Thrombocytopenia‡	4.56	3.03	4.33	3.97
Pain‡	4.06	3.72	4.06	3.94
Febrile neutropenia‡	4.06	3.44	3.83	3.78
Constipation‡	4.00	2.92	4.42	3.78
Sepsis‡	2.78	4.67	3.72	3.72
Malnutrition‡	3.81	3.22	4.00	3.68
Leukopenia‡	4.67	3.69	2.42	3.59
Psychosocial issues‡	4.06	3.60	3.00	3.55
Tumor lysis syndrome	2.41	3.79	4.15	3.45
Palliative care‡	2.81	4.03	3.52	3.45
Hypertension‡	3.00	3.03	4.22	3.42
Mucositis (oral) ‡	3.69	3.47	3.00	3.39
Graft versus host disease after HSCT*‡	3.00	4.15	3.00	3.38
Virus reactivation after HSCT*‡	3.04	4.04	3.04	3.37
Varicella virus‡	2.78	3.47	3.77	3.34
Terminal care‡	2.64	4.09	3.27	3.33
Mucositis (gastrointestinal) ‡	3.25	3.69	2.92	3.29
Endocrine complications‡	2.68	3.33	3.68	3.23
PAC / VAP*; occlusion	2.83	3.23	3.60	3.22
Thrombosis	2.31	3.80	3.51	3.21
Menstruation	3.06	2.56	3.94	3.19
Sub-/infertility	3.19	4.36	2.03	3.19
Fatigue	4.11	3.17	2.28	3.19
Sinus thrombosis	1.94	4.17	3.43	3.18
Diabetes mellitus	2.17	3.34	3.97	3.16
Pancreatitis	2.00	4.25	3.06	3.10
Neutropenic colitis	2.00	4.06	3.09	3.05
Nephrological complications; tubular	2.64	3.21	3.24	3.03
Hyperviscosity syndrome	1.43	3.47	4.03	2.98
Superior vena cava syndrome	1.46	3.94	3.50	2.97

Table 2.1. Continued

	Mean score†			
Supportive care topic	Prevalence	Severity	Adequate treatment options	Overall mean score
Posterior reversible encephalopathy syndrome	1.86	3.97	2.97	2.93
Skin defect after radiotherapy	2.45	3.30	2.88	2.88
Cardiomyopathy	1.69	4.26	2.57	2.84
Nephrological complications; glomerular	2.12	3.33	2.97	2.81
Veno-occlusive disease	1.47	4.21	2.63	2.77
Disruption of taste	3.94	2.56	1.78	2.76
Extravasation of chemotherapy	1.36	3.91	2.77	2.68
Fever	2.58	2.83	2.52	2.65

† On a 5-point Likert scale ranging from 1 (low ranking) to 5 (high ranking).
‡ These items were included in round 2.
* PAC = port-a-cath, VAP = venous access port, HSCT = hematopoietic stem cell transplantation.

Table 2.2. Results of the Delphi survey round two, sorted by descending mean scores.

	Importance to develop a CPG*		
Supportive care topic	Mean score†	Median score†	Range†
Infection	4.61	5	3 – 5
Sepsis	4.33	5	2 – 5
Febrile neutropenia	4.28	5	2 – 5
Pain	4.17	4	2 – 5
Nausea / vomiting	4.14	4	2 – 5
Restrictions in daily life and activities	*4.06*	4	2 – 5
Palliative care	3.91	4	1 – 5
Procedural sedation	*3.86*	4	2 – 5
Terminal care	3.83	4	1 – 5
Mucositis (oral)	3.75	4	2 – 5
Varicella virus	3.64	4	2 – 5
Mucositis (gastrointestinal)	3.64	4	2 – 5
Malnutrition	3.61	4	2 – 5
Thrombocytopenia	3.50	4	1 – 5
Peripheral neuropathy	*3.39*	3	2 – 5
Anemia	3.33	3	1 – 5
Graft versus host disease after HSCT*	3.31	3	1 – 5
Leukopenia	3.29	3	2 – 5
Virus reactivation after HSCT*	3.23	3	1 – 5
*Osteoporosis / ANFH**	*3.22*	3	1 – 5

Table 2.2. Continued

	Importance to develop a CPG*		
Supportive care topic	Mean score†	Median score†	Range†
Allergic reactions	*3.19*	3	1 – 5
Constipation	3.08	3	1 – 5
Hypertension	3.08	3	1 – 5
Endocrine Complications	3.03	3	1 – 5
Psychosocial issues	2.94	3	2 – 5
Hemorrhagic cystitis	*2.89*	3	1 – 4
Lung function disorder	*2.86*	3	1 – 5
Ototoxicity	*2.72*	3	1 – 4
Hypertriglyceridemia	*2.69*	3	1 – 5
Alopecia	*2.36*	2	1 – 5

† On a 5-point Likert scale ranging from 1 (low ranking) to 5 (high ranking).
* CPG = clinical practice guideline, HSCT = hematopoietic stem cell transplantation, ANFH = avascular necrosis of the femoral head.

Note: items highlighted in italic were written additions.

The mean scores for each supportive care topic of round one are presented in Table 2.1. In round one, 16 topics had mean scores below 2.5 on one of the three questions and were therefore eliminated (see Table 2.1). The 20 highest scoring topics were included in round two, as well as all written additions. There were 10 written additions: allergic reactions, alopecia, hemorrhagic cystitis, hypertriglyceridemia, lung function disorder, osteoporosis / avascular necrosis of the femoral head, ototoxicity, procedural sedation, peripheral neuropathy, and restrictions in daily life and activities.

After Delphi round two the panelists determined the following topics to be prioritized in upcoming development of CPGs: 1) infection, 2) sepsis, 3) febrile neutropenia, 4) pain, 5) nausea / vomiting, 6) restrictions in daily life and activities, 7) palliative care, 8) procedural sedation, 9) terminal care and 10) oral mucositis (Table 2.2).

Regarding the first nine topics of this top 10 there was agreement between panelists, i.e. more than 66% of all panelists rated a four or five on the 5-point Likert scale of that topic. Few panelists scored these items with a one or two, ranging from 0% (infection) to 14.3% (procedural sedation). With regard to the level of agreement, the intraclass correlation coefficient of the 20 topics presented in both round one and two was 0.904 (95% CI = 0.824-0.960, $p<0.001$) for round one and 0.918 (95% CI = 0.849-0.966, $p<0.001$) for round two. Thus, in both rounds agreement between panelists was very good, with a minor increase from round one to round two.

We explored differences in prioritized topics between the panel groups. Topics that were in the top 10 of all panel-groups (pediatric oncologists, general pediatricians and pediatric oncology nurses) were sepsis, infection, febrile neutropenia, nausea / vomiting and pain (Table 2.3). In addition to the previously mentioned topics, the top 10 topics of pediatric oncologists were: procedural sedation, palliative care, terminal care, osteoporosis / avascular necrosis of the femoral head and gastroenteral mucositis. For general pediatricians these were: restrictions in daily life and activities, palliative care, terminal care, oral mucositis and leukopenia. For pediatric oncology nurses these were: restrictions in daily life and activities, oral mucositis, varicella virus, graft versus host disease after hematopoietic stem cell transplantation and gastroenteral mucositis.

Table 2.3. Comparison of top 10 topics and corresponding scores between pediatric oncologists, general pediatricians involved in care for childhood cancer patients and pediatric oncology nurses.

	Pediatric oncologists	*Mean*	*General pediatricians*	*Mean*	*Pediatric oncology nurses*	*Mean*
1	Procedural sedation	4.38	*Sepsis*	4.73	*Infection*	4.91
2	*Infection*	4.36	*Infection*	4.64	*Nausea / vomiting*	4.55
3	*Febrile neutropenia*	4.21	*Febrile neutropenia*	4.45	*Pain*	4.55
4	*Nausea / vomiting*	4.07	Restrictions in daily life and activities	4.36	*Sepsis*	4.55
5	*Pain*	4.07	*Pain*	3.91	Restrictions in daily life and activities	4.36
6	Palliative care	4.00	Palliative care	3.82	Mucositis (oral)	4.27
7	Terminal care	3.93	*Nausea / vomiting*	3.82	*Febrile neutropenia*	4.18
8	*Sepsis*	3.86	Terminal care	3.73	Varicella virus	4.09
9	Osteoporosis / ANFH*	3.64	Mucositis (oral)	3.64	Graft versus host disease after HSCT*	3.91
10	Mucositis (gastrointestinal)	3.64	Leukopenia	3.55	Mucositis (gastrointestinal)	3.91

Note: items highlighted in italic are in the top 10 topics of all three panel-groups.

* ANFH = avascular necrosis of the femoral head, HSCT = hematopoietic stem cell transplantation.

2.5 DISCUSSION

In this study we performed a survey by use of the Delphi approach to prioritize supportive care in childhood cancer topics for the development of nationwide CPGs. Based on two rounds the panelists determined that the following topics are most important for future CPG development: infection, sepsis, febrile neutropenia, pain, nausea / vomiting, restrictions in daily life and activities, palliative care, procedural sedation, terminal care and oral mucositis. The top three topics show overlap, i.e. are all concerning infectious diseases, and underline the importance of this field in the childhood cancer population. Although sepsis and febrile neutropenia might be considered as subtopics of infection, both these topics are distinct enough to require their own guideline. These topics will be the starting point for our project to evolve supportive care in childhood cancer in the Netherlands from expert opinion to evidence-based medicine. This project will comprise both the development and implementation of supportive care CPGs and aims to identify gaps in knowledge to set up a research agenda for the next decade.

For our survey we used the Delphi approach. By groupwise feedback in successive questionnaires, panelists are informed of the groups' collective opinion. This might help them to identify topics that they missed or thought were unimportant, which thereby facilitates the opportunity for panelists to change their opinions.[22] In our Delphi survey, we did this by ranking the topics in round two according to the mean scores in round one. To ensure that all panelists were aware of this feedback, we explicitly and repeatedly communicated the ranking method of the round two questionnaire to all participating panelists via email. The Delphi approach eliminates potential disadvantages of the more informal methods of reaching consensus (e.g. committees), such as domination of the powerful individual or leading expert.[23] In addition, a Delphi survey is quick, cheap and has few geographical limitations.[24] Previous studies have shown that with the Delphi approach a small panel of similarly trained experts is sufficient to develop reliable criteria that inform judgment and support effective decision-making.[25]

Naturally a Delphi approach also has limitations. The feedback to panelists in the Delphi approach is limited to rearranging topics based on scores in a previous round. Therefore panelists do not have the opportunity to explain ones rationale for their decision to each other. Thus members are solely facilitated to change their opinion based on groupwise feedback, and not on individual arguments. This might be eliminated by organizing face-to-face meetings, where panelists can explain and discuss their choices. However, to our opinion this would undermine one of the fundamentals of the Delphi approach (anonymity) and might influence ones frame of reference (e.g. general

pediatricians making decisions based on stem cell transplantation patient arguments). Moreover it might give room to reintroduce the domination of the powerful individual or leading expert, a disadvantage that is eliminated by using the Delphi approach. Another possible limitation of the Delphi approach is that a true consensus may not be reached.[26] Although agreement in our Delphi survey was very good, there is still room for a substantially diverging opinion. Finally, a Delphi survey is as good as its participating panelists and their knowledge regarding the included topics. In our study we strived for a diverse as possible panel, while maintaining sufficient expert knowledge.

A Delphi survey can consist of two to an unlimited number of rounds, where researchers ought to seek results that realistically reflect consensus among panelists, without causing fatigue of panelists or depletion of resources. It is believed that the right balance is found in a Delphi survey of two or three rounds.[22] Classically, the first round is unstructured and seeks an open response, followed by a number of consecutive rounds where quantification of earlier findings is sought through rating or ranking techniques.[27] In our survey, and as described and performed in other studies, we choose to combine the 'classic' round one and two, where we asked panelists to rate items the core research group had devised but also invited them to suggest topics they thought were missing.[11,28] We asked all panelists to rate items on prevalence, severity and adequate treatment options as it has been clearly described that those are among the criteria for developing guidelines.[29] In the second and last round, we asked all panelists to rate items (which were rearranged according to rating from round one) for the importance of the development of a CPG.

It should be noted that the Delphi approach should not be viewed as a scientific method for creating new knowledge, but rather as a process for making the best use of the collective wisdom of participants.[23] Thus, the findings of a Delphi survey should be considered as expert "communis opinio", rather than as an indisputable fact.[27] In addition, in this study the Delphi survey does not have a selective character, i.e. it will not decide which CPG will or will not be developed. Rather it has a prioritizing character, where it should be viewed as a starting point in the development of CPGs for supportive care in childhood cancer. Naturally, we aim to develop these CPGs in an international collaboration, so as to prevent dual/overlapping work and to take advantage of international expertise and effort.

For this survey, we composed an expert panel which comprised pediatric oncologists, pediatric oncology nurses and general pediatricians involved in care for childhood cancer patients. It has been noted that including experts with different perspectives on a problem produces a better performance than a homogeneous group.[27] In the near

future, we intend to also assess the importance of the various supportive care topics using focus groups of patients and parents/caregivers of patients. In these focus groups, patients and parents/caregivers will be able to express in their own words experiences, prioritization issues and expectations regarding (guidelines for) supportive care in childhood cancer.[30] In doing so, possible gaps in our guideline framework might be identified. For this Delphi survey we chose not to include patients, parents and caretakers as we intended to first assess the professional needs for CPGs.

There were differences between pediatric oncologists, general pediatricians and pediatric oncology nurses in the prioritization of topics. There might be various reasons for these differences. For instance, one can think of the more intensive bed-side contact that pediatric oncology nurses have with the children as opposed to pediatric oncologists, therefore worrying more about topics that are of daily concern for patients and parents, e.g. restrictions in daily life and activities. Pediatric oncologists on the other hand may focus more on the process of the disease, hereby emphasizing worry on other topics, such as palliative care. By letting both groups participate and also inviting general pediatricians involved in care for childhood cancer patients, we believe that our final prioritization list is a good reflection of the general clinical importance for guidelines for supportive care in childhood cancer.

2.6 CONCLUSION

In this study we performed a survey by use of the Delphi approach to prioritize supportive care in childhood cancer topics for the development of nationwide CPGs. After two rounds, the 10 topics with the highest rating on the importance to develop a CPG were infection, sepsis, febrile neutropenia, pain, nausea / vomiting, restrictions in daily life and activities, palliative care, procedural sedation, terminal care and oral mucositis. With this study, we have taken the first step towards the development of Dutch evidence-based guidelines for supportive care in childhood cancer, which we believe are crucial to further decrease mortality and especially morbidity and to improve quality of life among childhood cancer patients. We aim to develop these CPGs in an international collaboration, therefore we welcome all experts who are currently working on CPGs in supportive care in childhood cancer or who are willing to contribute to the initiative. Even though currently performed nationally, we believe that this study can be regarded as an example starting point for international development of CPGs in the field of supportive care in cancer, or any other field for that matter.

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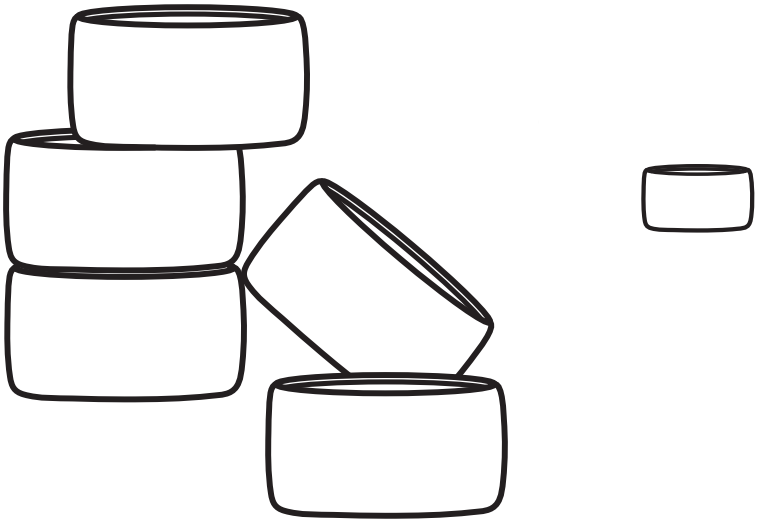
SUPPLEMENTAL MATERIALS

The following supplemental materials are available online:

2/S1 Full results from both Delphi Survey Rounds (7 pages)



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